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Azaindole synthesis through dual activation catalysis with N-heterocyclic carbenes†

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A convergent, transition-metal-free synthesis of 2-aryl-azaindoles has been developed. The interception of a reactive aza-*ortho*-azaquinone methide intermediate by an acyl anion equivalent generated through carbene catalysis provides high yields, a wide substrate scope, and the synthesis of previously inaccessible azaindoles.

The azaindole and diazaindole heteroaromatic scaffolds possess medically significant biological activity despite limited presence in known natural products.[1] In particular, C2-aryl azaindole compounds show potent and selective inhibition of a variety of kinases over-expressed in virulent human-cancer cell lines (Fig. 1).[1,2] Additionally, specific C2-aryl azaindoles selectively inhibit anthelmintic activity, agonize melatonin receptors, and downregulate expression of inflammatory cytokines.[3,4] In many cases, azaindoles can have superior pharmacokinetics when compared to other heterocyclic compounds.[4b] From an industrial standpoint, more than 100 patents containing bioactive C2-aryl azaindoles exemplify the pharmacophore potential of this scaffold. The continued interest in developing these molecules underscores the need for robust synthetic methods to access these structures in order to drive current and future research efforts.

Several classic methods for the synthesis of this heterocycle currently exist and are analogous to established indole technology. The most common is the Sonogashira-type synthesis,[2c,e,f,5] which shows a broad scope for controlled C2-arylation in excellent to poor yields.[6] While generally dependable, this method struggles or fails to generate azaindoles with hetero-, bromo-, or densely functionalized aromatic C2 substituents.[6c,7] The Larock synthesis (Fig. 2b) yields 2,3-disubstituted azaindoles in a moderately reliable fashion but can provide limited yields and regiocontrol.[2d,8] Both methods depend on transition metal catalysts and alkyne-containing starting materials.

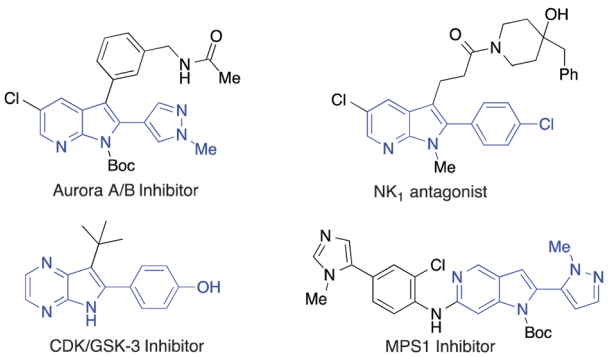

Fig. 1 Selected biologically active 2-aryl-azaindoles.

Other existent methods emanating from Hegedus–Mori–Heck,[9] Fischer,[10] or Madelung[11] approaches use palladium and strongly basic or acidic conditions with high temperatures. Many syntheses do not provide access to substitution of the C2-aryl moiety or the full scope of azaindole regioisomers. Various milder, non-traditional synthetic routes have been reported, but afford multiple azaindole regioisomers and/or display poor regiocontrol.[12] While current methods allow access to a moderately diverse array of C2-aryl azaindoles, complimentary organocatalytic approaches with an emphasis on convergency and substitution variability would be important to improve access to these essential molecular scaffolds.

In our program to explore the versatility and power of N-heterocyclic carbenes[13] (NHCs) for new catalytic reactions, we recently discovered a novel and efficient synthesis of C2-aryl indoles through reaction of a transient aza-*ortho*-quinone methide[14,15] with an acyl-anion equivalent. We hypothesized that the analogous aza-*ortho*-aza-quinone methide intermediate **1*** could be intercepted to form the related azaindole core **3** (Table 1a). As benzaldehyde derivatives are diverse and widely available, the success of this method could broaden the scope of C2-aryl substitution in a concise and efficient manner. Additionally, this proposed organocatalytic approach would compliment the known transition-metal catalysed syntheses.

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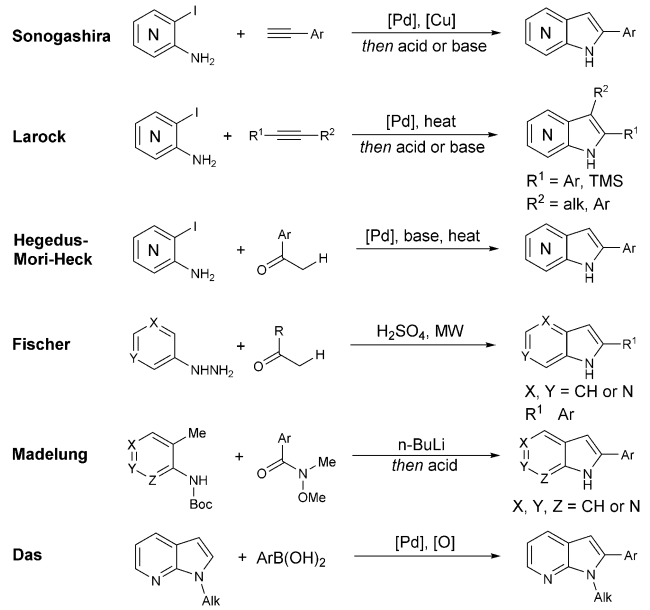
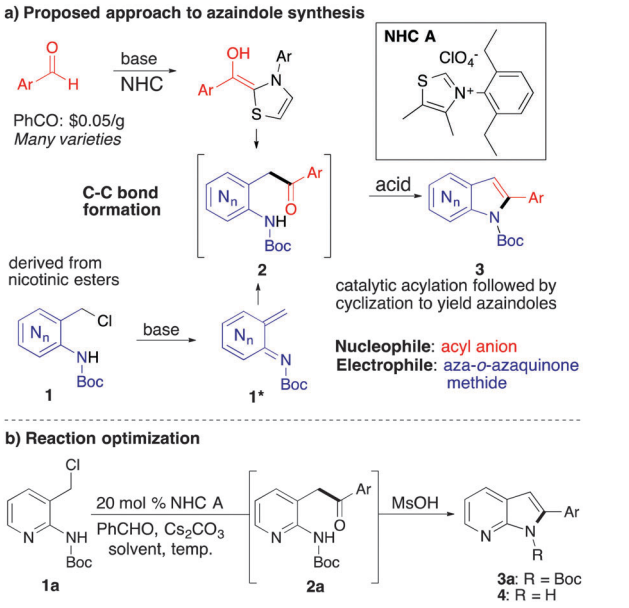


Fig. 2 Common approaches to C2-substituted azaindoles.

Table 1 Reaction approach and optimization



Entry[a]	Solvent	% Cat.	Equiv. MsOH	Temp. (°C)	2[b] (%)	3[b] (%)	4[b] (%)
1	THF	20	—	rt	78	—	—
2	Dioxane	20	—	rt	96	—	—
3	Diethyl ether	20	—	rt	59	—	—
4	MTBE	20	—	rt	64	—	—
5	2-Methyl THF	20	—	rt	66	—	—
6[c]	Dioxane	10	—	rt	68	—	—
7[d]	Dioxane	5	—	rt	Trace	—	—
8[c]	Dioxane	5	—	45	Trace	—	—
9	THF	20	6.5	rt	70	0	0
10	Dioxane	20	6.5	rt	30	36	38
11[e]	**Dioxane**	**20**	**7.5**	**rt, then 40**	**0**	**0**	**90**

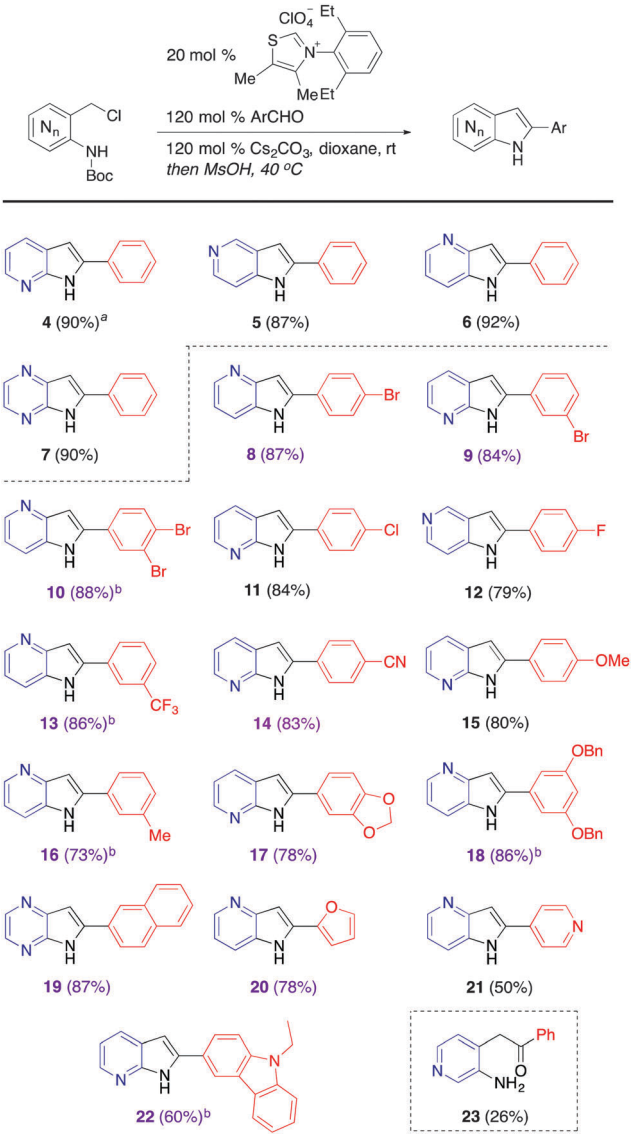
[a] Optimization reactions conducted on a 0.04 mmol scale (0.1 M) using 20% catalyst, 1.2 equivalents of aldehyde, and 1.2 equivalents of Cs_2CO_3 unless otherwise noted. [b] Yield of isolated material. [c] Conducted at 0.2 M concentration. [d] Conducted at 0.4 M concentration. [e] Conducted on a 0.4 mmol scale; cyclization reaction went to completion overnight.

Our initial investigations took aza-*ortho*-azaquinone methide precursor, picolyl chloride **1a**, benzaldehyde and NHC A with cesium carbonate as base (Table 1b). This mixture yielded aryl-ketone **2a**, analogous to the ketone intermediate observed in our indole-synthesis.[15] A range of ethereal solvents were found to support the NHC-catalyzed acylation in good to excellent yields with a catalyst loading of 20 mol% (entries 1–5). Attempts to lower catalyst loading proved unproductive even at increased concentration or temperature (entries 6–8). With optimized conditions for ketone formation, we turned our focus to optimizing the dehydrative cyclization to afford the azaindole core in a one-pot operation. A survey of cyclization conditions revealed that methanesulfonic acid enables cyclization of ketone **2a** in dioxane (entry 10). This cyclization fails in other more Lewis-basic ethereal solvents, as is illustrated in entry 9. Further optimization revealed an additional equivalent of acid and mild heating promotes complete conversion of ketone **2a** to deacylated azaindole **4** in excellent yield. Attempts to selectively deliver boc-protected azaindole **3a** by varying reaction conditions revealed de-acylation occurs concomitantly with the dehydrative cyclization.

With optimized conditions in hand, we turned our focus to surveying the reaction scope with variation of the azaindole core (Table 2). We found that 4-, 5-, 7-, and 4,7-di-azaindoles with 2-phenyl substitution (**4–7**) could be delivered in excellent yields. Attempts to synthesize 2-phenyl-6-azaindole were unsuccessful and only produced **23**; the acylation reaction was found to proceed in poor yield, and treatment with acid in dioxane or CH_2Cl_2 led only to removal of the carbamate protecting group to yield **23**. Further investigation into the reduced yield of **23** revealed competing decomposition of the picolyl chloride starting material to reaction conditions.

We then turned our focus to survey the scope of substituted benzaldehydes. Aryl aldehydes with *p*-, *m*-, and di-*p*,*m*-bromine substitution afforded azaindoles **8–10** in excellent yields. Of note is the synthesis of azaindole **10**; to the best of our knowledge, it has never been reported and would be difficult to synthesize using transition-metal catalyzed methods due to competing insertion reactions. The developed method also functions well with aldehydes bearing chlorine (**11**) and fluorine (**12**) substitution. Use of other aldehydes with *ortho* substitution besides hydrogen groups proved unproductive, putatively due to steric clash of the substitution with the catalyst.[15a,17] Benzaldehydes containing other electron-withdrawing groups, such as those with *m*-trifluoromethyl and *p*-cyano substitution, resulted in the efficient synthesis of azaindoles **13** and **14**, respectively. The use of aryl aldehydes with electron donating substituents in the *meta* and *para* positions afforded azaindoles **15–18** in high yields. Finally, polycyclic aromatic aldehydes (**19**) and, in fair to good yields, heteroaromatic aldehydes (**20–22**) were competent substrates. Further expansion of aldehyde scope towards use of non-aryl aldehydes have proved unproductive to date. Additionally, the use of secondary alkyl aldehydes afforded trace amounts of acylated product and a complex mixture of

Table 2 Exploration of reaction scope



[a] Purple denotes a previously unreported azaindole. [b] Denotes an unreported azaindole with substitution never before reported on any (di-)azaindole regioisomer.[16]

unknown reaction products. The use of cinnamyl or crotyl aldehydes yielded no detectable product.

In addition to the current substrate scope, multiple recrystallization techniques to yield pure azaindoles have been developed. Initially, aqueous work-up and silica gel chromatography successfully yielded 2-phenyl-7-azaindole **4**. However, we observed poor solubility of most unprotected azaindoles in common chromatographic solvents, rendering standard isolation difficult. Further investigation showed that a basic workup followed by recrystallization from DCM through slow addition of toluene or hexanes afforded the azaindole products in high purity and yield. This purification method takes advantage of the limited solubility of the synthesized compounds and the minimal formation of insoluble side-products/byproducts. The general cleanliness of the reaction was studied by NMR spectroscopy and LCMS for azaindole **4**, revealing nearly full conversion of azaindole precursor to product. For this reaction, the only discernable impurity in greater than 5% yield in NMR spectra of the unpurified material after basic work up was benzoin.

In conclusion, we have developed an efficient method for the transition-metal-free synthesis of azaindoles. This method provides access to a range of 2-aryl azaindole regioisomers as well as to diazaindoles. A broad scope of *meta*- and *para*-functionalization on the C2 aryl substituent is tolerated, including halogens, other electron-withdrawing groups, and electron-donating groups. The azaindole products were purified through an aqueous workup followed by recrystallization or column chromatography. To the best of our knowledge, this is the first synthesis of the full regioisomeric family of azaindoles employing mild temperature and conditions without transition metal catalysis. Further expansion of NHC-catalyzed dual activation strategies to access functionalized heterocycles are underway.

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